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Bio-Chemical Study of New Mannich Bases and Their Complexes with (Cu^{+2}, Fe^{+2}, Zn^{+2}, Hg^{+2})

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ABSTRACT

In the present study, a series of mannich bases were synthesized by reaction between diketone compounds and ammonia or amine derivatives to give enamino ketone as intermediate, which may react with aldehyde compounds to yiled compounds [1-5], and complexes[6-9]. The newly synthesized compounds[1-9] structures are characterized by{(C.H.N)–analysis, H-NMR-spectra, FT.IR-spectra}, stochiometric study, molar conductance, melting points, antimicrobial study. The data obtained gave good support for synthesized compounds [1-9].

Keywords: Enamine, complexes of mannich, Complexes (Cu^{+2},Fe^{+2}, Zn^{+2} ,Hg^{+2}).

INTRODUCTION

Mannich bases have become important starting material for synthesis of vari*ousorganic compounds.* Mannich reaction is an aminoalkylation reaction of aldehyde to yield enamine compounds ,they are class of compounds well known for along time & still continue the object of considerable interest ,mainly due to their pharmacological activities[1-3], technological applications in polymer industry specially as paints & surface –active reagents and other applications in different fields[4-7].

However its derivatives have long been used for their antibacterial, anti fungal activity[8-10], it is also an important analytical reagent due to its chelating ability ,further the complexation of mannich bases with metal ions may enhance their antimicrobial

properties and may also be used as potent drugs in the treatment of infectious diseases[11-13].

The original synthesis of mannich bases [1-9] are diketone compounds react with amonia or amine derivatives to give anaminoketons as intermediates ,activating mathylene group these intermediate are react with aldehyde compounds to yield final product of compounds [1-9], this reaction is highly regiospesific .

EXPERIMENTAL

- All chemical used where supplied from Fluka& Merck-chemical company.
- All measurement where carried out by :
  - Melting points: Electro thermal 9300, melting point Engineering LTD, U.K .
  - FT.IR-spectra: fourrier transform infrared shimadzu (8300), (FT.IR), KBr-disc was used.
  - H.NMR-Spectra in DMSO-solvent, in ppm unit, &(C.H.N)-Analysis.

Synthesis of compound [1]

A solution of 5,5–dimethy-cyclohexyl – 1,3 –dione (0.4 mole , 56 gm) was condensed with P-N,N-dimethyl benzaldehyde (0.2 mole, 29.8 gm) and ammonia (0.2 mole, 7 gm), the precipitate was filtered and recrystallized to yield 79% of compound [1] .

Synthesis of compound [2]

A solution of 2,5 – hexan –dione (0.4 mole, 45.6 gm) and p-methyl mercaptobenzaldehyde (0.2 mole, 30.4 gm) with ammonia (0.2 mole, 7 gm) was refluxed, after cooling, the precipitate was filtered and recrystallized to yield 81% of compound [2] .

Synthesis of compound [3]

A mixture of 2-mercapto benzothiazole (0.2 mole, 33.4 gm) with morpholone(0.2 mole, 17.4 gm) and formaldehyde (0.2 mole, 6 gm) was refluxed in ethanol, the precipitate was filtered and recrystallized to yield 85% of compound [3].

Synthesis of compound [4]

A mixture of 5,5 –dimethyl cyclohexyl -1,3-dione (0.2 mole, 28 gm) was reacted with 2-amino thiazole (0.2 mole, 20 gm) in presence of ethanol, the precipitate was filtered and recrystallized to give 78%of compound[4].

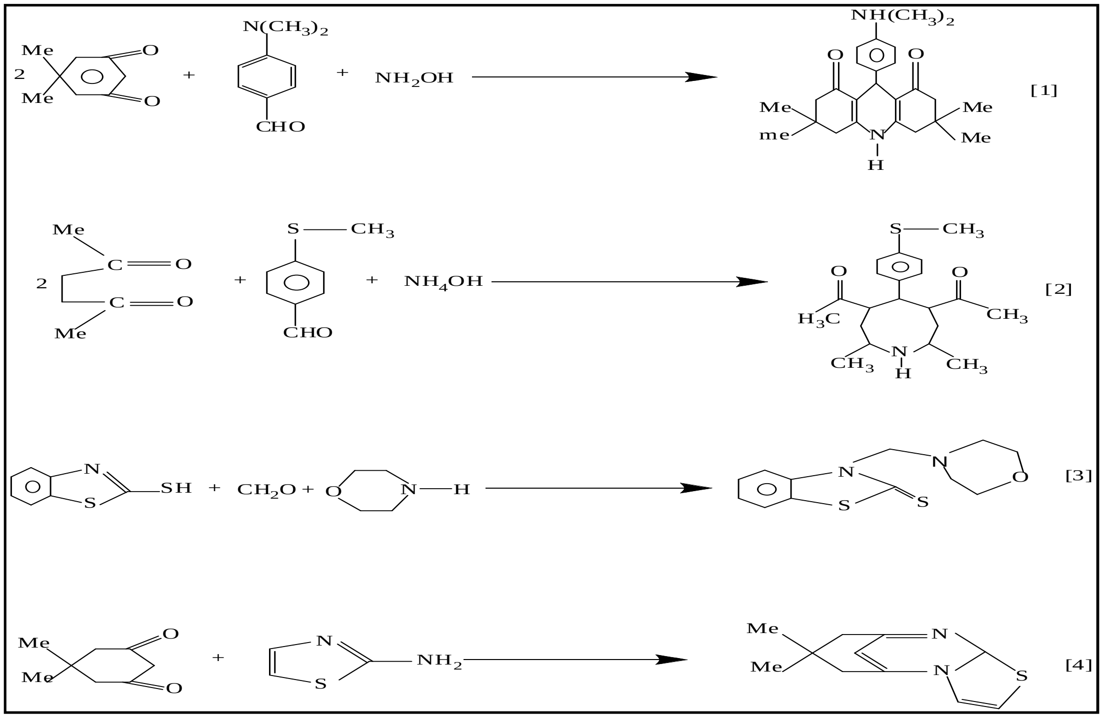
Synthesis of compound [5]

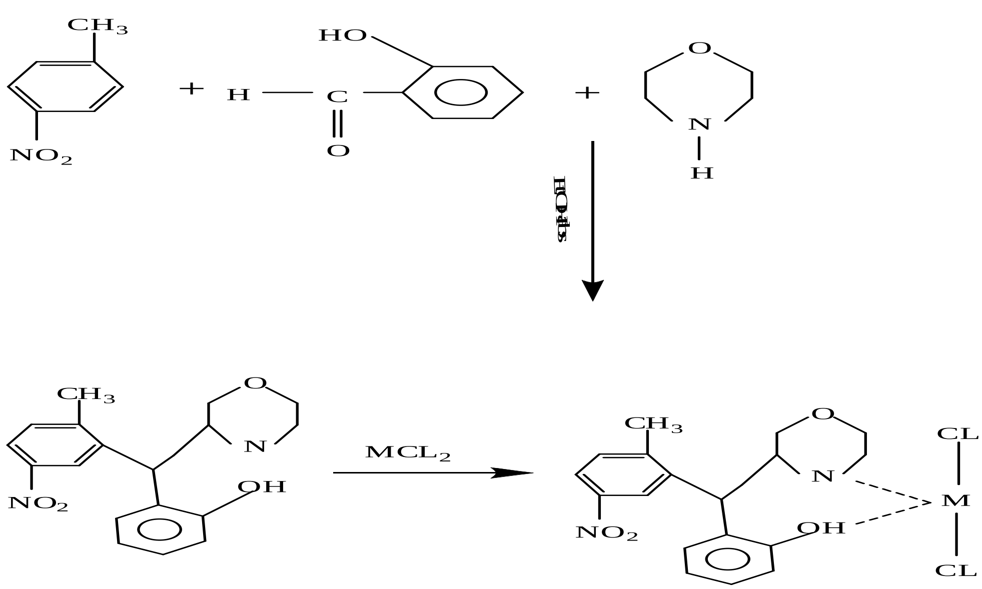
A mixture equimolar (0.01 mole) of (p-nitro tuloune 1.37 g, morpholine 0.87 g, salicyldehyde 1.22 g) were reacted in presence of 100 ml absolute ethanol, the mixture was continuously strrid with magnetic stirrer for getting a precipitation, after (24)hrs filtered, dried and crystallized to yield 84%.

Synthesis of complexes [6-9]

The hot ethanolic solution (30) ml of ligand (compound 5) (0.01 mole) was added to ethanolic solution (30) ml of (0.01 mole) metal chloride(Cu^{+2}, Fe^{+2}, Zn^{+2}, Hg^{+2}) respectively with mechanical stir for half hour, the solid complexes formed, filtered to give complexes with (Cu^{+2},Fe^{+2}, Zn^{+2}, Hg^{+2}) respectively.

Reaction Scheme:





Compound[5]

complexes[6-8]

Table (1) : FT.IR data (cm^{-1}) of compounds [1-9]

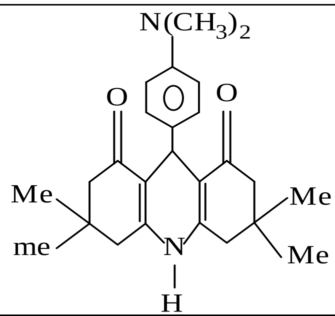
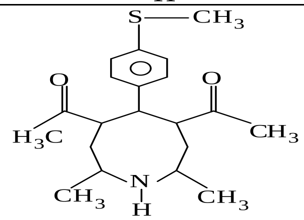
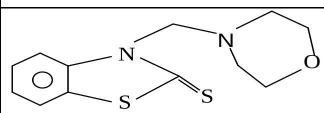
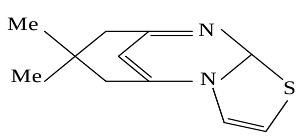
Comp. No.	Structural formula	Name of compounds	Only (Importance groups)
[1]		1,4-dihydro-{4-(N,N-dimethyl benzene)-2,3,5,6-bis (dimethyl cyclohexanone)}-pyridine.	□(N-H):3440 ,($-\overset{O}{\overset{\|}{C}}-$)of ketone : 1718S , (C-N)endo cycle of pyridine :1538, 1569, 4-N(Me)$_2$:Aromatic :1373
[2]		1,4,5,6-Tetra hydro –{5-(methyl phenyl sulphide) -2,8-dimethyl-4,6-di acetoazine.	□(N-H):3338 , ($-\overset{O}{\overset{\|}{C}}-$)of ketone :1735, (S-CH$_3$): 1411, (C-N)endocycle:1537
[3]		3-methylene Morpolone -2-thione –benzothiazole .	(C-N)endo cycle:1537, (C-S)endocycle of thiazole: 729,(C-O-C) of morpholone : 1230
[4]		1,2-(thiazolino)-4,6-(5,5-dimethyl cyclo hexane)-2-hydropyrimidine	(C=N)endocycle of pyrimidine : 1577 S, (C-S)endocycle of thiazole: 740
[5]	$C_{18}H_{20}N_2O_4$	4-nitro-2-(morpholinesalicyl) tuloune	(C-O-C) of morpholone: 1232, (OH):3417, (NO$_2$): 1350
[6]	Cu ($C_{18}H_{20}N_2O_4$) Cl_2	complex	(C-O-C) of morpholone: 1235, (OH):3425, (NO$_2$): 1340, (M-O):555, (M-N): 450, (M-Cl):393
[7]	Fe ($C_{18}H_{20}N_2O_4$) Cl_2	complex	(C-O-C) of morpholone: 1236, (OH):3420, (NO$_2$): 1350, (M-O):551, (M-N):445, (M-Cl):384
[8]	Zn ($C_{18}H_{20}N_2O_4$) Cl_2	complex	(C-O-C) of morpholone :1230, (OH):3428,(NO$_2$): 1345, (M-O):540, (M-N):440 ,(M-Cl):380
[9]	Hg ($C_{18}H_{20}N_2O_4$) Cl_2	complex	(C-O-C) of morpholone :1236, (OH):3420,(NO$_2$): 1347, (M-O) :530, (M-N):432 ,(M-Cl):370

Table (2) : Physical properties& Elemental Analysis of compounds [1-9]

Comp. No.	M.F	M.P (C°)	$\Omega^{-1}.cm^2.mol^{-1}$	Calc./Found. C%	H%	N%	M	Cl
[1]	$C_{25}H_{32}N_2O_2$	178	--	76.530 76.428	8.163 8.113	7.142 7.029	---	---
[2]	$C_{20}H_{25}NO_2S$	171	--	69.970 69.804	7.288 7.113	4.081 4.006	---	---
[3]	$C_{12}H_{14}N_2OS_2$	165	--	54.135 54.037	5.263 5.123	10.526 10.417	---	---
[4]	$C_{11}H_{14}N_2S$	157	--	64.077 63.968	6.796 6.637	13.592 13.387	---	---
[5]	$C_{18}H_{20}N_2O_4$	160	--	65.853 65.697	6.097 6.001	8.536 8.477	---	---
[6]	$Cu\ (C_{18}H_{20}N_2O_4)\ Cl_2$	234	10.44	46.698 46.453	4.323 4.287	6.053 6.020	13.737 13.562	15.350 15.295
[7]	$Fe\ (C_{18}H_{20}N_2O_4)\ Cl_2$	244	17.51	47.488 47.376	4.397 4.243	6.155 6.041	12.278 12.138	15.609 15.526
[8]	$Zn\ (C_{18}H_{20}N_2O_4)\ Cl_2$	257	16.32	46.514 46.426	4.306 4.290	6.029 6.000	14.077 14.023	15.289 15.163
[9]	$Hg\ (C_{18}H_{20}N_2O_4)\ Cl_2$	218	15.68	36.024 36.010	3.335 3.200	4.669 4.514	33.487 33.416	11.841 11.811

Table (3): Antibacterial activity of the compounds[1-9] {diameter of zone (mm)}.

Compounds[1-9] *	diameter of zone(mm)	
	G+: Staphylococcus. aureus	*G-: E-Coli*
compounds[1]	13	8
compounds[2]	18	15
compounds[3]	15	13
compounds[4]	14	11
compounds[5]	14	9
complex[6]	30	25
complex[7]	27	22
complex[8]	29	25
complex[9]	29	23
*Minimum Inhibitory concentration (MIC)of compounds[1] (5mg/ml).		

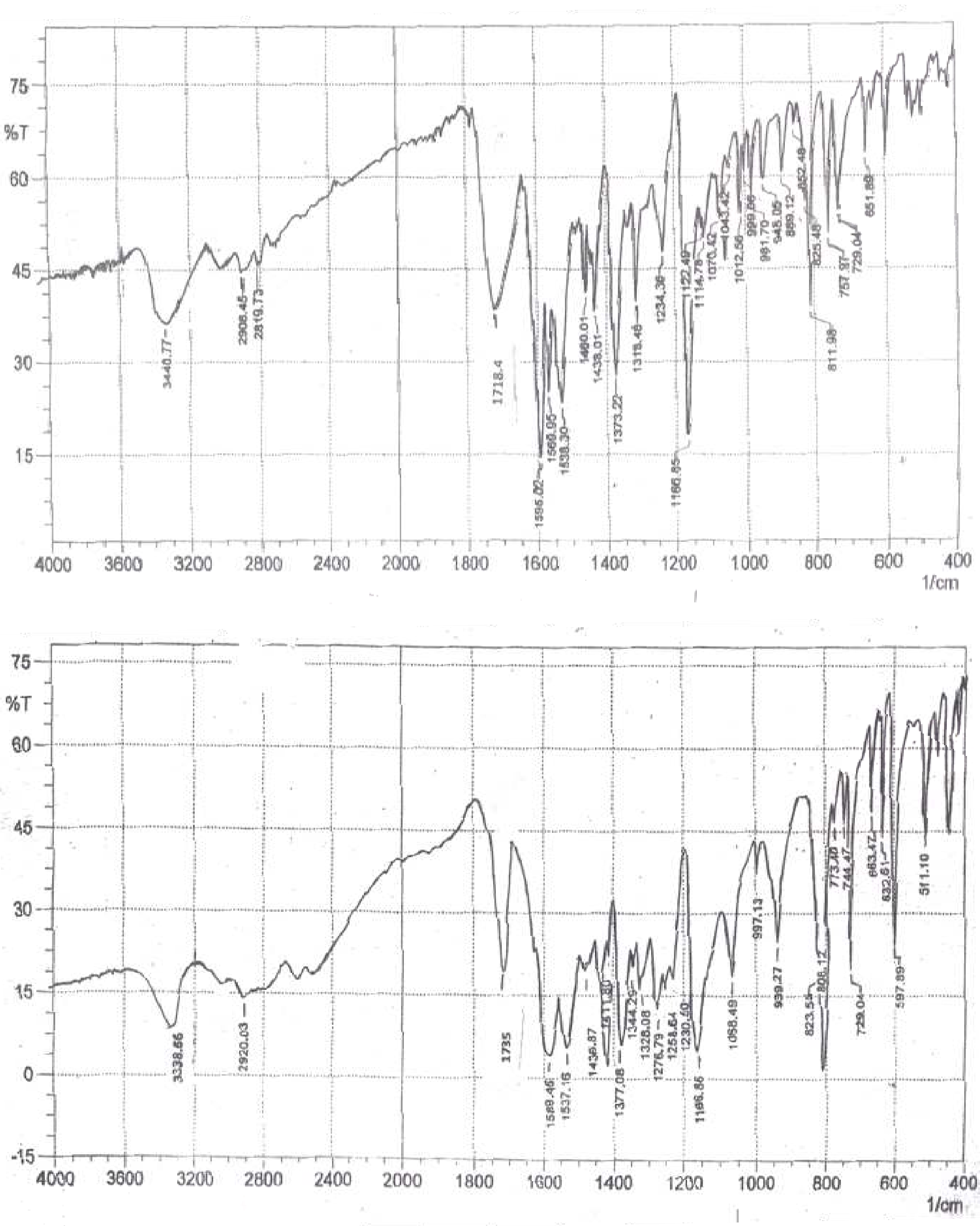


Fig (1,2):FT.IR-Compounds [1,2]

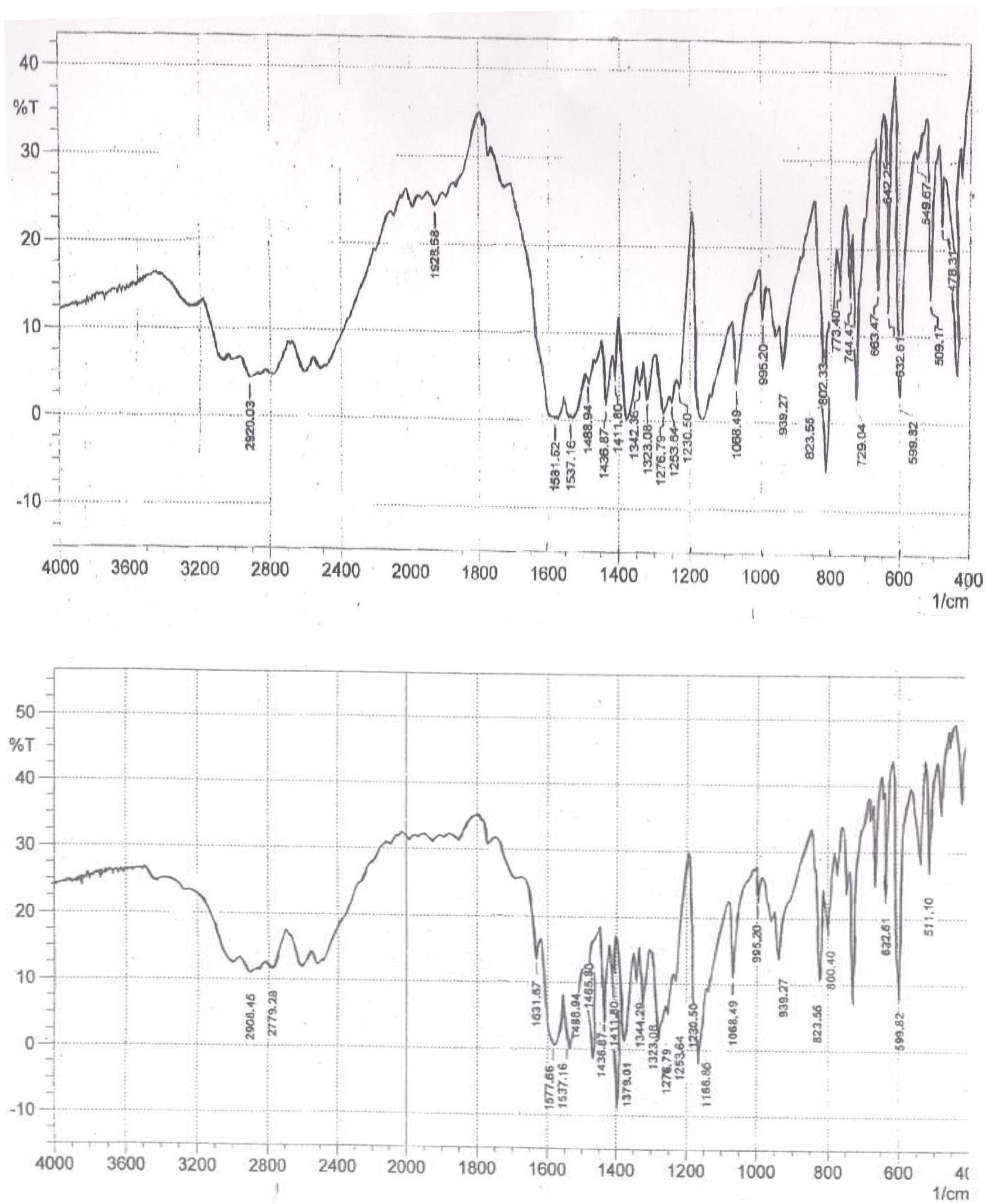


Fig (3,4):FT.IR-Compounds [3,4]

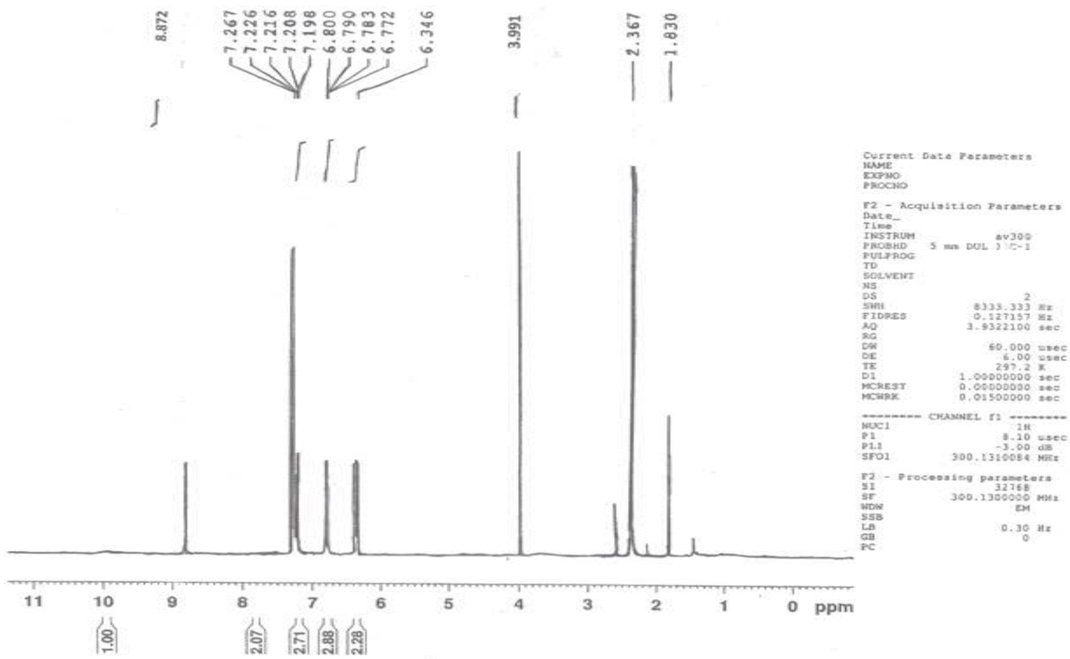


Fig (5):H.NMR-Compound [1]

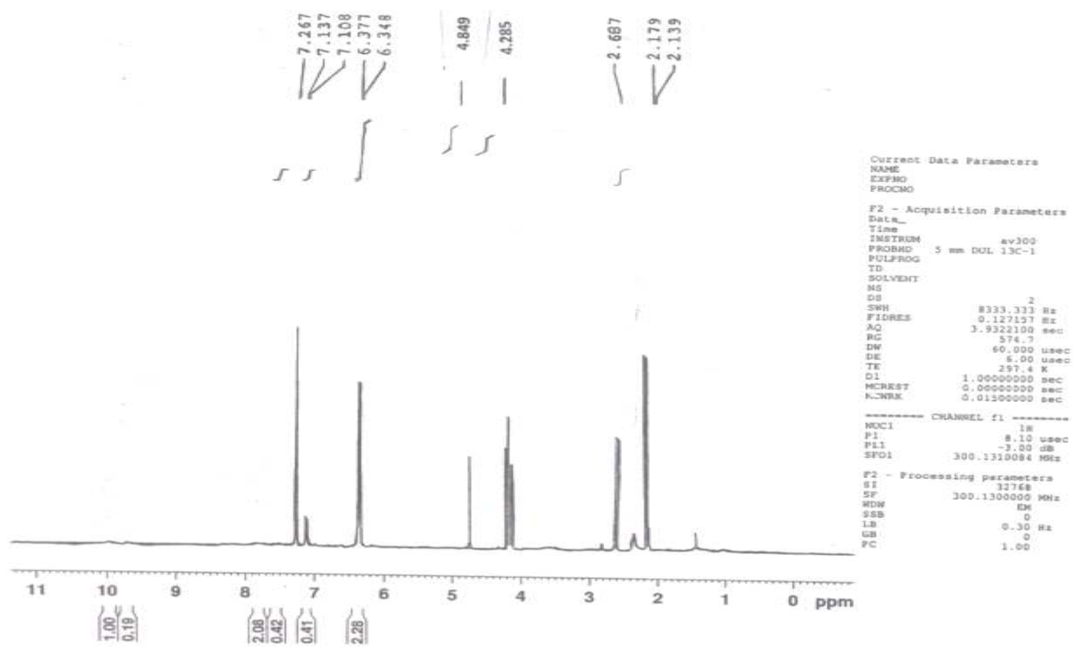


Fig (6):H.NMR-Compound [3]

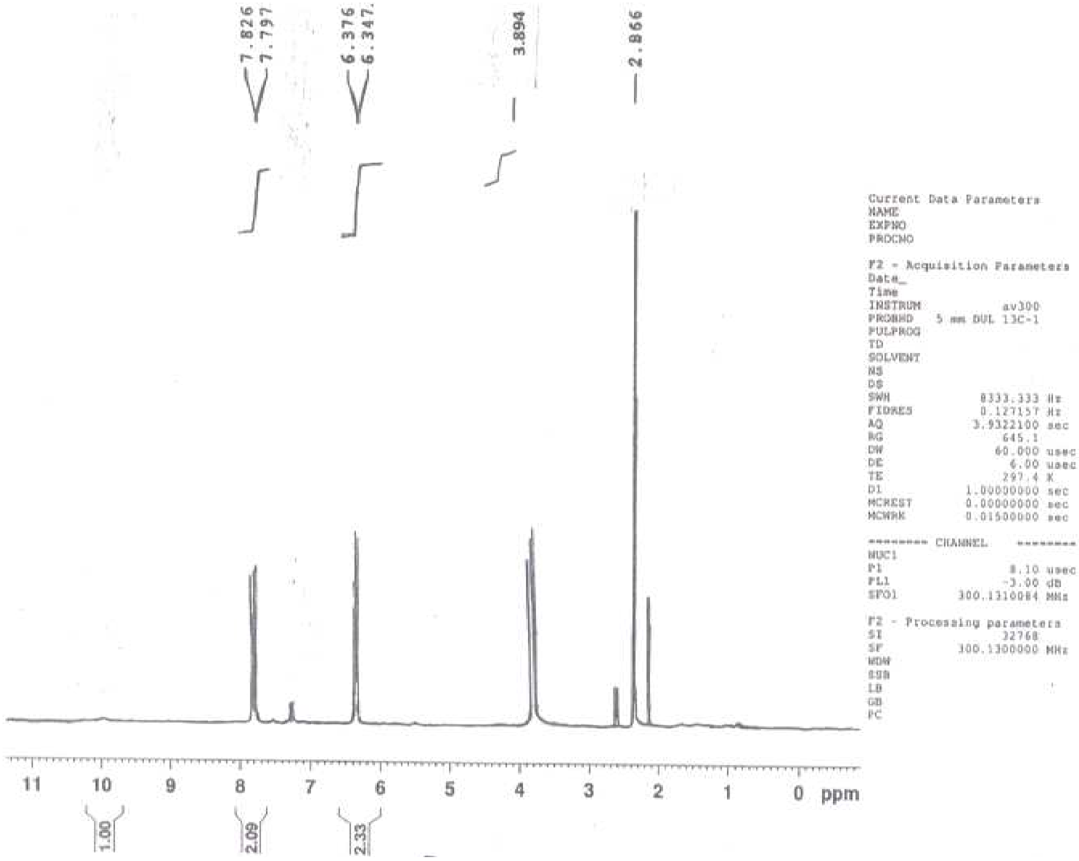


Fig (7):H.NMR-Compounds [4]

RESULTS AND DISCUSSION

All synthesized compounds [1-9] have been characterized by their melting points and spectroscopic methods(FT.IR-spectra, (C.H.N)-analysis H.NMR-spectra), stochiometric study of complexes, molar conductance, microbial study of complexes.

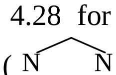
In FT.IR spectra ,the reaction is followed by appearance of absorption band at (3440) cm^{-1} due to (N-H) endo cycle of pyridine, band at(1718) cm^{-1} due to carbonyl of keton(-CO-) ,bands at (1538,1569)cm^{-1} is due to (C-N) endocycle of pyridine and band at (1373) $cm^{-1}$is due to (4-$N(CH_3)_2$) in compound[1], while compound[2] is appeare absorption band at (3338)cm^{-1} is due to (N-H) endocycle of pyridine , band at (1735) cm^{-1} is due to carbonyl of ketone (-CO-), band at (1587)cm^{-1} is due to (C-N) endocycle, and band at (1411)cm^{-1} is due to (S-CH)group[14,15], where as compound [3] ia appear absorption ban at (1537)cm^{-1} is due to (C-N) endo cycle , band at (1230)cm^{-1} is due to (C-O-C)[15] of morpholone cycle & band at (729)cm^{-1} is due to (C-S) endo cycle[(14)] of thiazole , while compound [4] is appear absorption band at (1577)cm^{-1} is due

to (C=N) endo cycle[14] of pyrimidine & band at (740)cm^{-1} is due to (C-S) endo cycle[14,17] of thiazole .Compound[5] appeared band at (1350)cm^{-1} due to ($-NO_2$), band at (3417) cm^{-1} due to (OH)[16] of phenol, band at (1232)cm^{-1} due to[15] (C-O-C) of morpholine, while some of these bands shifted in their complexes of compounds[5] with ions (Cd^{+2}, Ni^{+2}, Mn^{+2}) and other bands appeared such as (M-O[16,2], M-N, M-Cl).

And other data of functional groups show in the following, table (1) and figures(1-4) .]

H.NMR- Spectrum of compounds [1-4] showed : singlet signal at 8.87 for proton of (N-H) group , signal at 7.26 for proton of pyridine cycle & signal at 3.99 for six proton of dimethyl group ($N(CH_3)_2$) in compounds [1] .

Singlet signal at 4.63 for protons of methy group (S-CH) [14,15] , doublet Signal at 7.78 for para protons of phenyl (ph-S) , and signal at 8.69 for proton of (N-H) in compound [2].

Signal at 4.84 for protons of (` )[14] of morpholone cycle and signal at 4.28 for protons of methylene group[15] of () in compound [3] .

Signal at 6.37 for proton of pyrimidine cycle C_4-H and signal at 7.82 for proton of thiazole in compound [4] , and other peaks shown in the following , figures (5-7).

(C.H.N)–analysis, from compared the calculated data with found data of these compounds, the results were comparable , the data of analysis , M.F and melting points are listed in table (2).

From spectral results (H.NMR, FT.IR, C.H.N), stochiometric of complexes (M:L) (1:1) by using (mole ratio and job)-methods and molar conductance of compound[5] as a ligand with(Cu^{+2},Fe^{+2}, Zn^{+2} ,Hg^{+2})are assigned that the ligand is bi dentate , coordination through nitrogen of morpholine and the (OH)-group of phenol, due to 4-coordinated tetrahedral geometry.

Assay of antimicrobial activity[2]:

Antimicrobial activity was tested by the filter paper disc diffusion method against gram positive bacteria *(Staphylococcus .aureus)* and gram negative bacteria (*E-Coli*) , 0.1 ml of the bacterial suspensions was seeded on agar. To determine minimum inhibitory concentration(MIC) for each compounds[1-9] were ranged between (1-10)mg/ml by dissolved in (DMSO) .

The positive results or sensitivity were established by the presence of clear zone of inhibition around active compounds which were measured with a meter rule and diameters were recorded based on (mm), the assays were performed with two replicates.

Generally, The results showed that the compounds[1-9] have great inhibitory effect against tested bacteria.

Table (3) showed the zone of inhibition of the compounds[1-9] in this study ranged (from 30 to 8) mm. From results, we noted that the complexes[6-9] have higher antibacterial activity against *S.aureus and E-Coli* is due to the presence of ions(Cu^{+2},Fe^{+2}, Zn^{+2}, Hg^{+2}) in thier structures. Consequently, these compounds become more effective in precipitating proteins on bacteria cell walls, and presence of heterocyclic ring in these compounds which increase microbial activity, destroying

the cell membranes, these compounds had abroad antibacterial activity[18]

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